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Is therapeutic use of atropine eye drops to slow myopia progression in children scientifically recognized and is it proven to be effective?

O uso terapêutico do colírio de atropina para retardar a progressão de miopia em crianças é reconhecido cientificamente e possui eficácia comprovada?

¿El uso terapéutico del colirio de atropina para retardar la progresión de miopía en niños está reconocido científicamente y posee eficacia comprobada?

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ABSTRACT

The prevalence of myopia worldwide has been increasing significantly over the past decades, and it is currently a leading cause of visual impairment worldwide. This severe and significant public health problem has been addressed at the community level with the use of atropine eye drops at a concentration of 0.01% (one drop daily). This regimen appears to offer an appropriate balance between costs and benefits, indicated by a 50% reduction in the annual myopia progression rate in children without resulting in clinically significant adverse effects. The therapeutic use of atropine eye drops to slow myopia progression in children is scientifically recognized and it has been proven to be effective.

Keywords:
Myopia;
Child;
Epidemiology;
Atropine;
Myopia/Complications

RESUMO

A prevalência da miopia vem aumentando significativamente em todo o mundo ao longo das últimas décadas e é hoje uma das principais causas de deficiência visual, globalmente. Para enfrentar esse grave e relevante problema de saúde pública, a comunidade oftalmológica conta hoje com o uso do colírio de atropina na concentração de 0,01% (1 gota diária). Esse regime terapêutico parece oferecer uma relação custo/benefício apropriada, representada pela significativa redução de 50% na taxa anual de progressão da miopia em crianças, sem desencadear efeitos adversos clinicamente significantes. O uso terapêutico do colírio de atropina para retardar a progressão de miopia em crianças é reconhecido cientificamente e possui eficácia comprovada.

Palavras-Chave:
Miopia;
Criança;
Epidemiologia;
Atropina;
Miopia/Complicações

RESUMEN

La superioridad de la miopía viene aumentando significativamente en todo el mundo a lo largo de las últimas décadas y es hoy una de las principales causas de deficiencia visual en todo el mundo. Para enfrentarse a ese grave y relevante problema de salud pública, la comunidad oftalmológica cuenta hoy con el uso del colirio de atropina en la concentración del 0,01% (1 gota diaria). Ese régimen terapéutico parece ofrecer una relación costo-beneficio apropiada, representada por la significativa reducción del 50% en la tasa anual de progresión de la miopía en niños, sin desencadenar efectos adversos clínicamente significantes. El uso terapéutico del colirio de atropina para retardar la progresión de miopía en niños está reconocido científicamente y posee eficacia comprobada.

Palabras Clave:
Miopía;
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1. Myopia is a severe public health problem

Overall, myopia is the leading cause of distance vision loss [1,2,3,4]. In 2010, myopia affected 1.4 billion people, corresponding to 27% of global population [3]. Considering that the number of people with myopia should continue to increase in absolute and relative numbers, it is estimated that 2.5 billion people will be affected by myopia in 2020 [4].

Among adolescents and young adults in Korea, Taiwan, and China, myopia prevalence varies between 84% and 97% [5,6,7]. In contrast to Western populations, in which myopia prevalence is low (<5%), the prevalence in Asian children aged ≤8 years is significantly higher. In Singapore, it is reported to be 9%–15% in school-aged children; 24.7% in children aged 7 years; 31.3% in children aged 8 years, and 49.7% in students aged 9 years [8,9]. Among school children aged 12 years, myopia prevalence is 62% in Singapore and 49.7% in Guangzhou, China, compared with 20% in the United States, 11.9% in Australia, 9.7% in urban areas of India, and 16.5% in Nepal [8].

The significant increase in myopia prevalence worldwide indicates that the pathogenesis of myopia is determined by a series of environmental factors and behavioral characteristics [10,11] and that the environment strongly influences the development of myopia. However, the strong association of myopia with family history [12] and heredity in the nonsyndromic forms of myopia, particularly in high myopia (–5.00 diopters (D) or more), indicates that >50% of the variability of refractive errors within populations is determined by genetic factors [13,14,15,16]. In addition, Genome-Wide Association studies identified >20 loci associated with myopia, and preliminary results suggest that the genes associated with refractive errors can increase in number significantly by modifications in body weight, insulin metabolism, and fatty-acid metabolism, and that these genetic factors may influence growth regulation and neurotransmission [17].

There is evidence that the overall increase in myopia prevalence is accompanied by the increase in myopia severity [5]. Vitale et al. [18], found that the prevalence of moderate myopia in the United States (between –2.00 D and –7.90 D) increased almost 2-fold (from 11.4% in 1971–1972 to 22.4% in 1999–2000), and the prevalence of high myopia (greater than –8.00 D) increased 8-fold in the same period (from 0.2% to 1.6%). The overall prevalence of high myopia (greater than –5.00 D) was 2.9% (224 million people) in 2010 [5].

High myopia (greater than –6.00 D and an axial length ≥26 mm) is associated with an increased risk of blindness-inducing conditions such as myopic macular degeneration, retinoschisis, posterior staphyloma, glaucoma, retinal detachment, and cataract [19,20,21]. The prevalence of visual loss by pathological myopia was 0.1%–0.5% in Europe and 0.2%–1.4% in Asia [21]. Yamada et al. (2010) found that 12.2% cases of visual impairment were caused by pathological myopia in a Japanese population [22]. Myopic macular degeneration is the leading cause of monocular blindness in Tajimi, Japan [23] and it is currently the primary cause of blindness in Shanghai, China [24]. The absolute risk of visual impairment is 30% in individuals with an ocular axial length of 26 mm, and it increases to 95% among those with an axial eye length of ≥30 mm [25,26].

Brazil has a population of 201 million, and the estimated prevalence of myopia and degenerative myopia is 22–72 million and 2–7 million, respectively [27].

The total annual economic cost of myopia is estimated at USD 268 billion [17]. In addition to the cost of myopia correction, we should consider the risk of visual loss caused by eye diseases that are more prevalent in individuals with myopia, including glaucoma, cataracts, and retinal detachment [19,20,21,22,23,24]. As part of the strategy to address this severe public health problem, the World Health Organization has chosen myopia as one of its five priorities, and has included myopia in the "Global Initiative to Eliminate Avoidable Blindness" [28].

Without the adoption of effective interventions to control myopia progression, the prevalence of pathological myopia is expected to continue to increase. At present, myopia prevalence worldwide is approximately 3%, and a high percentage of these individuals may develop myopic choroidal neovascularization, which is the leading cause of progressive visual loss [21]. The current options for controlling the rate of myopia progression include conservative and pharmacological interventions [29]. The efficacy of conservative regimes, except orthokeratology, is relatively small [30]. The effectiveness of pharmacological intervention is much higher, especially that of treatment regimens employing topical atropine [31].

2. Topical atropine to slow myopia progression in children

Brondstein et al. (1984) [32], conducted follow-up observations up to age 9 years (mean age of 4 years and 3 months) in 253 individuals with myopia who were subjected to an instillation regimen of one drop of 1% atropine daily to slow myopia progression. In a comparison

of myopia progression rate in this group to that of a control group of 146 individuals with myopia, the rate decreased during the treatment period. Upon treatment discontinuation, the rate was similar in both groups. However, starting with the ATOM study [33] —a randomized clinical trial involving 400 Asian children—use of atropine was effective in delaying myopia progression. In this study with a 2-year follow-up, the authors found that the myopia progression rate decreased 75% with topical 1% atropine and found no severe side effects. A systematic Cochrane review [29] of studies involving atropine reported that the annual myopia progression rate could be decreased from –0.80 D to –1.00 D with the use of atropine 0.5% and 1.0%, respectively.

Topical atropine eye drops decreased the annual myopia progression in children by decreasing the rate of eye elongation (axial length) [29,33,34,35,36].

Chia et al. [34] evaluated children subjected to a 5-year treatment with atropine eye drops to control myopia progression; in this study, children used atropine at 0.5%, 0.1%, and 0.01% for 2 years and, 1 year after washout, atropine at 0.01% for 2 additional years. Children treated with atropine at 0.5% and 0.1% showed a higher rate of myopia progression in the washout year (rebound effect). Children who received atropine at 0.01% experienced a lower rebound effect during the washout year and myopia progression was significantly delayed in the 2-year treatment after the washout year, with a noticeable reduction of adverse effects, including the need to use photochromic lenses for higher-dose atropine (0.5% and 0.1%). Children treated with atropine 0.01% had minimal pupillary mydriasis (0.8 mm), minimum loss of accommodation (2–3 D), and did not require the use of progressive lenses.

Polling et al. [31], (2016) evaluated 77 children with myopia who completed 1 year of follow-up under the treatment regimen of one drop of 0.5% atropine daily. This European study showed that 0.5% atropine might be an effective treatment for progressive myopia. The average myopia progression rate before the intervention year was –1.0 ± 0.7 D/year. The use of 0.5% atropine decreased the rate of progression to –0.1 ± 0.7 D/year during treatment. Despite the high frequency of adverse events (82.9%), most children maintained therapy for the entire study period. The main adverse effects were photophobia (72.4%), problems with reading (37.7%), and headache (22.4%).

Huang et al. [37] (2016) conducted a meta-analysis to evaluate the efficacy and effectiveness of 16 interventions in slowing myopia progression in children. Its main findings were as follows:

1) High-dose atropine (1% and 0.5%), moderate-dose atropine (0.1%), and low-dose atropine (0.01%) showed clear effects in slowing myopia progression (all statistically significant); pirenzepine, orthokeratology, contact lenses that change the peripheral defocus, cyclopentolate, and ophthalmic bifocal prismatic lenses showed a moderate effect (all statistically significant except for cyclopentolate and ophthalmic bifocal prismatic lenses); progressive ocular lenses, bifocal ocular lenses, ocular lenses that change the peripheral defocus, and more outdoor activities showed a weak effect (only progressive ocular lenses showed a statistically significant effect); rigid gas-permeable contact lenses, soft contact lenses, ocular hypocorrected lenses, and timolol were ineffective (all without statistical significance).

2) High-dose atropine (1% and 0.5%) was significantly more effective than the other interventions except for moderate-dose atropine (0.1%) and low-dose atropine (0.01%). Pairwise comparisons between bifocal ocular lenses, cyclopentolate, more outdoor activities, orthokeratology, progressive ocular lenses, ophthalmic bifocal prismatic lenses, contact lenses that change the peripheral defocus, ocular lenses that change the peripheral defocus, and pirenzepine showed no significant differences, except the benefit of orthokeratology compared to progressive ocular lenses. Rigid gas-permeable contact lenses, soft contact lenses, timolol, and ocular hypocorrected lenses were worse than other interventions, with no statistically significant differences within this group.

3) Asian children appear to have greater benefits from treatment than Caucasian children, and most interventions stopped showing an effect after the second year.

The authors believe that topical atropine has the greatest efficacy in slowing myopia progression [37]. However, atropine is rarely prescribed for the correction of progressive myopia in Western countries. The reasons may be the higher efficacy of treatment in Asia than in Europe [31]. or the possibility of severe and irreversible complications after prolonged atropine use, but this possibility is not

substantiated by literature [31]. The long-term effects of atropine were investigated in animal and human studies [38,39], and the potential photochemical damage to the retina because of pupillary mydriasis during prolonged daylight exposure has not been reported [40,41]. Therefore, daily atropine use appears to be safe even with prolonged durations [36,42].

Atropine is a potent nonselective antagonist of muscarinic receptors present in human ciliary muscle, retina, and sclera, and it is the best-studied pharmacological agent for slowing myopia progression [33].

However, the mechanism underlying the delay in myopia progression and the site of action of atropine are not known [43]. Initial studies suggest that the delay occurs via atropine effects on the accommodation of the crystalline lens, but recent studies indicate that it occurs via nonaccommodative mechanisms in the retina and sclera [44,45].

In the retina, amacrine cells express muscarinic receptors in the cell membrane [46]. The binding of atropine to these receptors could increase dopamine release, which is a chemical mediator involved in the inhibition of ocular growth [44]. Atropine decreased the retinal levels of the neurotransmitter γ-aminobutyric acid in mice with induced myopia [47]. Another hypothesis is the effect of atropine on the sclera. Scleral fibroblasts express muscarinic receptors on their cell membranes, and the binding of atropine to these receptors could affect scleral remodeling [48]. The effect of atropine on ocular growth probably does not occur via an accommodative mechanism because the inhibitory effect of atropine on ocular growth is also observed in chicks, in which the ciliary muscles are activated via nicotinic receptors instead of muscarinic receptors [44].

Recent studies have demonstrated that topical 0.01% atropine (one drop daily) in children is effective in slowing myopia progression and is safe, because this concentration induces clinical symptoms only in a few cases [34,37]. Furthermore, low-dose atropine (0.01%) is not associated with the intensity of the rebound effect observed with high-dose atropine (1%, 0.5%, and 0.1%). This characteristic makes low-dose atropine (0.01%) one of the most effective strategies in the management of myopia progression, although the results need to be replicated in other populations. Chia et al. [34] showed that children using low-dose atropine (0.01%) for 5 years had less myopia than children treated with higher doses, that the use of one drop of 0.01% atropine per day slowed myopia progression by 50% compared to untreated children, and that the use of this concentration was safe to children aged 6–12 years for up to 5 years; however, additional studies are needed to confirm these findings. Atropine (0.01%) caused minimal pupillary mydriasis (<1 mm), decreased sensitivity to light—experienced with higher drug concentrations—and did not cause difficulties in near vision, eliminating the use of progressive lenses.

In Brazil, atropine use to slow myopia progression is off-label. Therefore, all children subjected to treatment should be involved in a clinical study with a protocol approved by the ethics committee, and parents or legal guardians need to sign informed consent forms.

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